REMARKS

Claims 55, 56, 58-72, 74-87, and 99-102 are pending the present application. Claim 55 has been amended to harmonize the language of the claim. No new matter is added and no change in scope is intended. Upon entry of the present amendment, claims 55, 56, 58-72, 74-87, and 99-102 will remain pending.

I. The Claimed Inventions Are Not Obvious

Claims 55, 56, 58-72, 74-87, and 99-102 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over the combination of U.S. Patent No. 5,463,564 (hereinafter, the "Agrafiotis reference"), Uhlmann *et al.*, *Chem. Rev.*, **1990**, 90, 543-584 (hereinafter, the "Uhlmann reference") and U.S. Patent No. 5,639,603 (hereinafter, the "Dower reference") taken further in view of U.S. Patent No. 5,720,923 (hereinafter, the "Haff reference") or U.S. Patent No. 5,650,122 (hereinafter, the "Harris reference"). Applicants traverse the rejection and respectfully request reconsideration because the subject matter of claims 55, 56, 58-72, 74-87, and 99-102 is neither disclosed nor suggested by the collective teachings of the cited references.

To establish prima facie obviousness, the references relied upon must teach or suggest all the elements of the claimed subject matter. M.P.E.P. § 2143.03 (citing In re Royka, 180 U.S.P.Q. 580 (C.C.P.A. 1974)). The claims recite "generating *in silico* virtual compounds," "evaluating *in silico* a plurality of virtual compounds," "generating a library of nucleobase sequences *in silico*," "evaluating *in silico* a plurality of virtual compounds, " and "evaluating *in silico* a plurality of virtual nucleotides." Although the Office Action appears to suggest that the Agrafiotis reference teaches these steps, this simply is not the case.

The Agrafiotis reference utilizes a synthesis protocol generator to identify **reagents** that should be mixed together (Col 6, ll. 29-35). The synthesis protocol generator thus identifies a combination of reagents, not a virtual compound, a virtual nucleobase sequence, or a virtual nucleotide as recited in Applicants' claims. Mere instructions to add, for example, two reagents from a reagent repository together to synthesize a particular member of a directed diversity library does not constitute *in silico* evaluation as recited in Applicants' claims. Indeed, instructions to nail two boards together say little, if anything, about what a house containing such boards will look like. In the same way, the identification of mixing sequences of reagents says

little, if anything, about the structure of compounds that may be produced. Thus, contrary to the Office Action's assertion, the Agrafiotis reference does not disclose *in silico* evaluation of compounds.

The remaining references do not supply that which is lacking from the Agrafiotis reference, nor does the Office Action contend that they do. In view of the foregoing, the claimed inventions are not obvious in view of the Agrafiotis reference and in view of the combination of other cited references. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

II. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 557-5963 if there are any questions regarding Applicants' claimed invention. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

55. **(Amended Three Times)** A method comprising:

generating *in silico* virtual compounds according to thermodynamic property, target accessibility, targeting to functional regions of target nucleic acid sequence, or uniform distribution to target nucleic acid sequence, wherein real compounds corresponding to said virtual compounds modulate the expression of a target nucleic acid sequence;

synthesizing compounds corresponding to at least some of said virtual compounds; and

robotically assaying said synthetic compounds for one or more desired physical, chemical or biological properties by computer-controlled polymerase chain reaction or by computer-controlled enzyme-linked immunosorbent assay.